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α-Adrenergic mediation of the tail skin temperature response to naloxone in morphine-dependent rats

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Studies were undertaken to evaluate the role of central noradrenergic neurons in the tail skin temperature (TST) surge that accompanies morphine withdrawal in the rat. A 5 °C increase in TST and a 1–2 °C decrease in rectal temperature (Tr) was observed following administration of a dose of naloxone HCl (NAL, 1 mg/kg, s.c.) which precipitated withdrawal in morphine-dependent rats. Intracerebroventricular (i.c.v.) injection of clonidine HCl, a partial α_2-adrenergic agonist did not alter TST in morphine-dependent animals. However, clonidine (10 or 50 μg/rat, i.c.v.) given 10 min prior to the administration of NAL completely blocked the TST response to the opiate antagonist in the morphine-dependent animals. Although NAL and clonidine reduced Tr to a similar extent in morphine-dependent rats, their effects were not additive when the drugs were administered sequentially. Treatment with the α-adrenergic antagonist phentolamine (11.9 or 60 μg/rat, i.c.v.) failed to alter TST when administered alone, but the highest dose significantly reduced the TST response to naloxone in the morphine-dependent rat. In addition, phentolamine, at high doses only, moderately reduced Tr, but the α-adrenergic antagonist failed to modify the decline in Tr associated with NAL-precipitated morphine withdrawal. Collectively, these data indicate that brain noradrenergic neurons play a role in the TST surge which accompanies NAL-precipitated morphine withdrawal, and that the TST and Tr responses can be dissociated in the morphine-dependent rat.

INTRODUCTION

There are numerous reports suggesting a role for endogenous opioids in modifying body temperature regulation[7,9]. The temperature responses of the rat to opioids depend upon the dose administered and whether or not the animal is restrained[9,23]. These temperature effects appear to be centrally mediated and may result from an alteration of the hypothalamic set point for temperature regulation[9]. The mechanism by which opioids modify the temperature regulatory system is still speculative; however, several studies have suggested an interaction with central catecholamines[13,14,31].

An interplay between the actions of morphine and catecholamine metabolism was first suggested by Gunne[14] when he demonstrated that chronic administration of morphine increased norepinephrine (NE) content in whole brains and brain NE concentration levels were decreased during morphine abstinence. Naloxone-precipitated morphine withdrawal in rats results in an increased turnover of brain NE early in withdrawal[12,30]. The increased turnover is correlated with an increase in withdrawal behavior[30]. Additionally, Aghajanian[1] has demonstrated that neurons of the locus coeruleus (LC) become hyperactive during naloxone-induced withdrawal in morphine-dependent rats and that administration of clonidine normalizes the LC activity. Tseng et al.[31] reported that clonidine reduces the opioid withdrawal symptoms in rats and Gold et al.[13] have extended these observations to opioid addicts. Thus, it appears that central catecholamine release (possibly from neurons which have cell bodies in the LC) plays a role in opiate withdrawal.

We have observed[16,18,28] that during opiate withdrawal in morphine-dependent rats there is a rise in tail skin temperature (TST) accompanied by a fall in

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core body temperature. We have also reported[28] that associated with this flush-like temperature response is a surge in luteinizing hormone (LH) secretion and a transient tachycardia. These physiological responses are similar in magnitude, duration and temporal patterns as those observed in women undergoing a menopausal hot flush[5,24,26,33,34] and thus have led us to propose the use of the morphine-dependent rat model to study the mechanism underlying the hot flush syndrome. α-Adrenergic agonists have been utilized in the treatment of menopausal flushing in women[8,25,33,34]. α-Adrenergic activation also is implicated in the naloxone-precipitated withdrawal in morphine-dependent rats[22,31]. The purpose of this study was to investigate the effects of stimulation or blockade of α-adrenergic receptors on the temperature changes associated with naloxone-precipitated withdrawal in the morphine-dependent rat.

MATERIALS AND METHODS

Female Charles River CD rats weighing 230–280 g were housed in stainless steel cages in a room maintained at 26 ± 1 °C and illuminated from 05.00 to 19.00 h daily. Food and tap water were provided ad libitum. The animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p.) and placed in a Kopf stereotaxic apparatus and were implanted with a single cannula (26 gauge stainless steel tubing, Small Parts, Miami, FL) in the lateral cerebral ventricle 4 days prior to experimentation. The coordinates, obtained from the stereotaxic atlas of König and Klippel[19], were anterior +5.0 mm; lateral 0.5 mm; and ventral 7 mm below the surface of the skull. A wire stylet was fitted into the outer guide cannula and remained in place until the experiments described below were performed. Following the experiments, rats were killed and brains were dissected to verify the location of the cannula.

Morphine dependency was produced in the rats by subcutaneous (s.c.) implantation of one pellet containing 75 mg morphine-free base (Merck, St. Louis, MO), 1.13 mg Magnesium Stearate (Fisher Chemical, Fair Lawn, NJ), 37.5 mg microcrystalline cellulose (Avicel, FMC Corporation, Philadelphia, PA) and 0.56 mg Cab-o-sil (Cabot, Boston, MA). Two days later, two additional morphine pellets were implanted. All pellets were compounded in our laboratory using an F.J. Stokes tablet maker. This treatment regimen has been shown previously to produce morphine dependency as measured by several testing procedures[28]. In all studies, animals were used once only. We have previously reported that ovariectomy for less than two weeks does not affect the TST response to naloxone (NAL) (1 mg/kg s.c.) in morphine-dependent rats[28]. Thus, to eliminate cyclic reproductive hormonal variations in the animals, all rats were bilaterally ovariectomized at the time of implantation of the first morphine pellet.

To specifically evaluate the role of central noradrenergic neurons in the TST response to NAL in morphine-dependent rats, the adrenergic drugs were administered intracerebroventricularly (i.c.v.). Initial studies were performed to determine the optimal interval time between administration of the adrenergic drugs and naloxone. Phentolamine (Regitine HCl, Ciba Pharmaceuticals, Summit, NJ) was administered to morphine-dependent rats at a dose of (50 μg/rat, i.c.v.) at either 10, 30 or 60 min prior to administration of naloxone HCl (NAL, 1 mg/kg, s.c.; Dupont Pharmaceuticals, Gosden City, NY). A volume of 4 μl was used for all i.c.v. administration and the vehicle in all studies was isotonic saline (SAL). Data from these preliminary studies demonstrated that a similar maximal effect in rectal and tail skin temperature (TST) was observed after administration of phentolamine at either 30 or 10 min prior to NAL. Thus for all subsequent studies the adrenergic drugs were administered 10 min prior to NAL. Although NAL mediates the TST response by a central mechanism[17], the s.c. route for administration of NAL was chosen to prevent the potential elevation in i.c.v. pressure of a second drug injection and to eliminate such effects of the subsequent removal and replacement of the stylet. Also, we have previously demonstrated that this route and dosage of NAL produces maximal TST responses in the morphine-dependent rat[18]. In the subsequent studies reported herein, phentolamine was administered to morphine-dependent rats at doses of 11.9, 30 or 60 μg/rat. Clonidine (CLON, Boehringer Ingelheim, Ridgefield, CT) was administered to morphine-dependent rats at doses of 0.53, 10 or 50 μg/rat. The dose ranges for CLON[6,32] and phentolamine[6,21] were chosen on the basis of their ability to alter body temperature following i.c.v. administration. All solutions administered

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Prior to the administration of drugs, animals were lightly restrained in wire mesh tunnel cages with a wooden floor. These cages were constructed in our laboratory and were designed to provide access ports for i.c.v. and s.c. drug administration and to prevent the thermic insulation of typical restraint cages. Tail skin temperature (TST) was measured with an YSI thermistor probe (no. 427) placed on the dorsal tail surface at approximately 2 cm from its base and held in place by adhesive tape. Rectal temperature (Tr) was measured with an YSI thermistor probe (no. 402) inserted 5 cm into the rectum and held in place by adhesive tape wrapped around the base of the tail. The temperatures were measured at 5-min intervals with a Model 46 Tuc tele-thermometer and Model 4002 switch-box. This procedure allows for repeated measurement of core body and skin temperatures without further handling of the animals. A 30-min acclimation period, during which TST and Tr were monitored every 10 min, was used to insure the temperature stability prior to drug administration. After the initial TST and Tr were recorded, the drug (or vehicle) was administered and temperatures were recorded every 5 min for the next 60 min in a room maintained at 25 ± 1 °C.

To statistically evaluate the TST and Tr response to the drugs, the following procedures were employed. Temperatures were converted to changes in TST or Tr with the initial temperature (prior to administration of NAL) assigned the value of 0. Changes in TST and Tr were determined for each animal and data were grouped by the drug treatment and the time after drug was administered. Except for one group, where the room temperature was elevated, initial temperatures did not differ significantly among groups in any of the studies. To evaluate the magnitude of the temperature response, the maximal change in TST (MAXΔTST) for each animal was determined regardless of the time of this peak response. The MAXΔ for TST usally occurred at 10–15 min after NAL administration. The MAXΔ for Tr was similarly determined and in all cases it was observed at 60 min after NAL administration. Analysis of variance

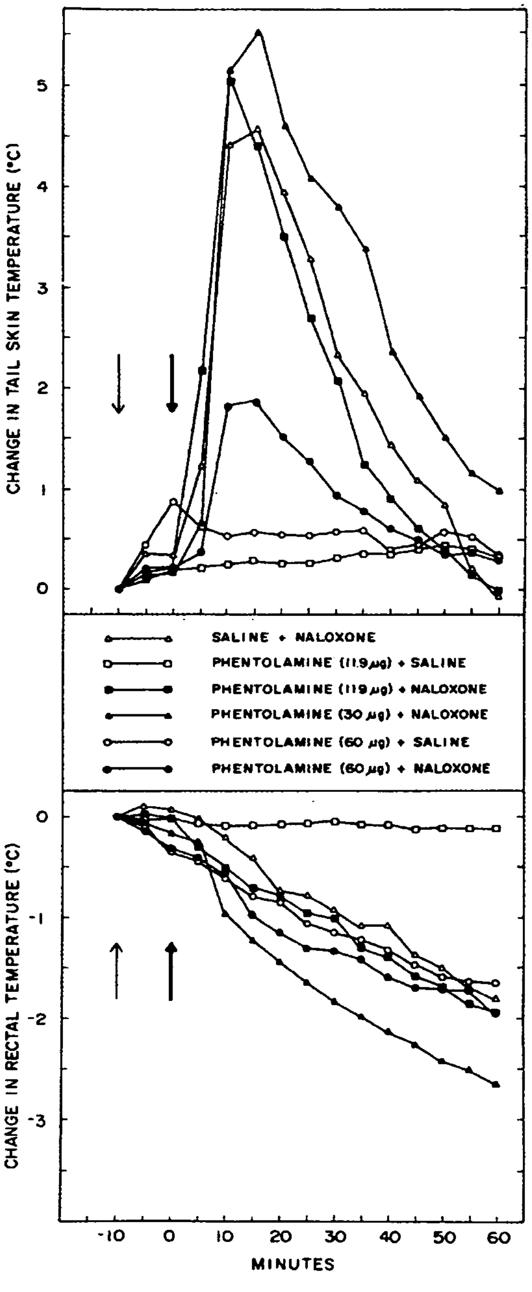

Fig. 1. Effects of phentolamine pretreatment on the response of TST and Tr to naloxone in morphine-dependent rats. Rats were administered phentolamine or saline, i.c.v. (small arrow, −10 min) and 10 min later received naloxone (1 mg/kg b. wt.) or saline s.c. (bold arrow, time 0). Represented here are the mean changes in TST and Tr for each group (n = 6 animals per group) at specific times after drug administration. Table I shows basal TST and Tr for the group of rats depicted in this figure. Additionally, in Table I the maximal changes in TST and Tr, irrespective of the time of that maximal response, are presented.

TABLE I

The effects of phentolamine on the TST and Tr responses to naloxone in morphine-dependent rats

Group	Treatment	Basal TST(°C)^a	Max Δ TST(°C)	Basal Tr(°C)^a	MAX ΔTr(°C)
A	Saline (4 μl, i.c.v.) + naloxone (1 mg/kg s.c.)	26.6 ± 0.2	4.8 ± 1.0*	37.9 ± 0.3	−1.8 ± 0.2
B	Phentolamine (11.9 μg, i.c.v.) + saline (1 ml/kg, s.c.)	26.8 ± 0.3	0.2 ± 0.2	38.1 ± 0.2	−0.2 ± 0.1**
C	Phentolamine (11.9 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	27.0 ± 0.3	4.9 ± 0.7*	37.5 ± 0.2	−2.0 ± 0.4
D	Phentolamine (30 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	27.1 ± 0.3	5.3 ± 0.4*	37.6 ± 0.5	−2.5 ± 0.3
E	Phentolamine (60 μg, i.c.v.) + saline (1 ml/kg, s.c.)	27.9 ± 0.5	−0.5 ± 0.5	37.4 ± 0.5	−1.5 ± 0.3
F	Phentolamine (60 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	27.0 ± 0.4	1.7 ± 0.9	37.0 ± 0.3	−1.7 ± 0.1

[a] Basal TST and Tr are those temperatures recorded just prior to administration of NAL.

*$P < 0.05$ vs groups B, E and F.

**$P < 0.05$ vs all other groups.

and Student, Newman–Keuls tests were used to evaluate the significance of differences among treatment groups. A probability level of $P < 0.05$ was chosen as significant for all tests.

RESULTS

Subcutaneous administration of NAL significantly increased TST and lowered Tr in morphine-dependent rats (Fig. 1, Table I). Administration of phentolamine at 11.9 or 30 μg failed to alter the TST or Tr response to NAL in the morphine-treated rats. Although pretreatment with 60 μg of phentolamine did not alter the Tr response to NAL, the TST response was significantly reduced to levels that were not different from that observed in controls (phentolamine and saline groups). Phentolamine treatment alone did not alter TST in the morphine-dependent rat whereas the highest dose of phentolamine (60 μg) produced a fall in Tr that was similar to that observed in the animals administered NAL.

As summarized in Fig. 2 and Table II, animals pretreated i.c.v. with either SAL or 0.53 μg CLON responded with a similar elevation in TST and fall in Tr following administration of NAL (1 mg/kg, s.c.). When the dose of CLON was increased to either 10 or 50 μg, the TST response to NAL was abolished in the morphine-dependent rats. However, the fall in Tr associated with administration of NAL was not affected by pretreatment with CLON. Interestingly, NAL or CLON (10 μg) treatment alone reduced Tr by about 2 °C, but when CLON treatment was followed 10 min later with NAL, Tr was reduced by only 1.3 °C. Except for the low dose of CLON, none of

TABLE II

The effects of clonidine on the TST and Tr responses to naloxone in morphine-dependent rats

Group	Treatment	Basal TST(°C)^a	Max Δ TST(°C)	Basal Tr(°C)^a	MAX ΔTr(°C)
A	Saline (4 μl, i.c.v.) + naloxone (1 mg/kg, s.c.)	26.9 ± 0.3	4.5 ± 0.8*	37.9 ± 0.4	−1.9 ± 0.2
B	Clonidine (10 μg, i.c.v.) + saline (1 ml/kg, s.c.)	27.2 ± 0.3	−0.05 ± 0.5	37.8 ± 0.3	−2.0 ± 0.1
C	Clonidine (0.53 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	27.1 ± 0.5	5.2 ± 0.3*	37.8 ± 0.2	−2.5 ± 0.3**
D	Clonidine (10 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	27.1 ± 0.5	0.05 ± 0.7	37.0 ± 0.4	−1.3 ± 0.1
E	Clonidine (50 μg, i.c.v.) + naloxone (1 mg/kg, s.c.)	28.2 ± 0.5*	0.5 ± 0.5	36.5 ± 0.5***	−2.4 ± 0.1

[a] Basal TST and Tr are those temperatures recorded just prior to administration of NAL.

*$P < 0.05$ vs all groups without asterisk.

**$P < 0.05$ vs group D.

***$P < 0.05$ vs groups A, B, and C.

MAX ΔTr(°C)
-1.8 ± 0.2
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-2.0 ± 0.4
-2.5 ± 0.3
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a	MAX ΔTr(°C)
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	-2.5 ± 0.3**
	-1.3 ± 0.1
*	-2.4 ± 0.1

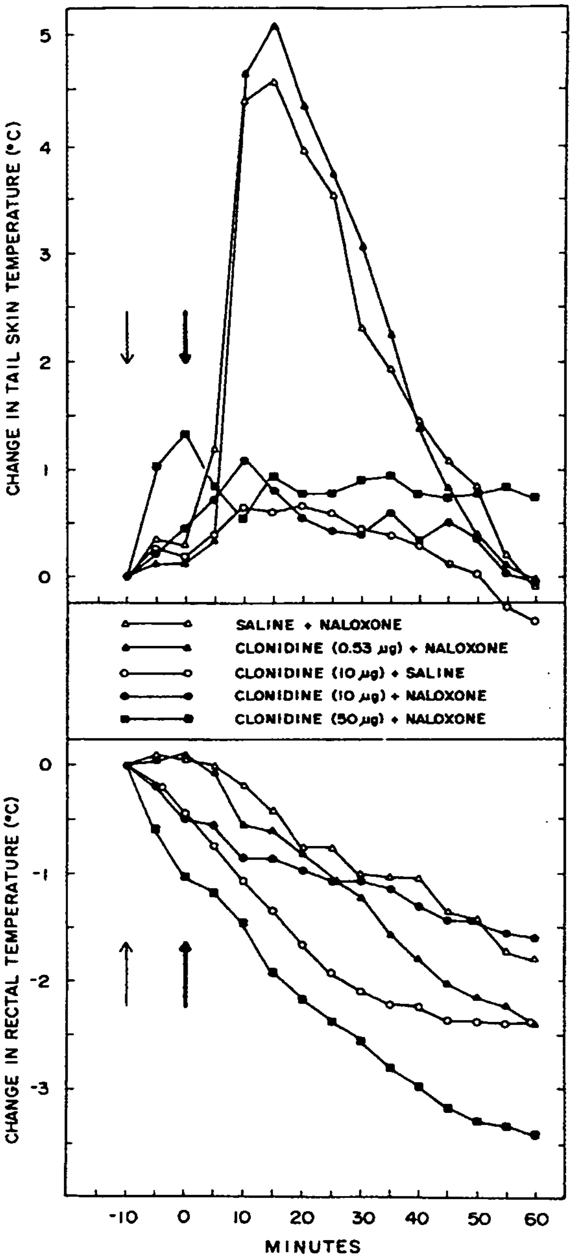

Fig. 2. Effects of clonidine pretreatment on the response of TST and Tr to naloxone in morphine-dependent rats. Rats were administered clonidine or saline, i.c.v. (small arrow, −10 min) and 10 min later received naloxone (1 mg/kg b. wt.) or saline s.c. (bold arrow, time 0). Represented here are the mean changes in TST and Tr for each group ($n = 6$ animals per group) at specific times after drug administration. Table II shows the basal TST and Tr for the groups of rats depicted in this figure. Additionally, in Table II are presented the maximal changes in TST and Tr, irrespective of the time of that maximal response.

the Tr responses of any other group were significantly different (Table II). Thus, it is clear that the decline in Tr in response to sequential administration of these two drugs was not additive.

DISCUSSION

We have previously shown that NAL-induced TST surges occur in concert with other physiological responses which are mediated by sympathetic neurons of the CNS[16–18,28]. In naive rats, morphine treatment reduces NE turnovers whereas administration of opiate antagonists to morphine-dependent rats causes a hyperactivity of noradrenergic neurons in several brain areas[1,2,20,30]. Biochemical studies have demonstrated an enhanced central NE turnover following administration of NAL to morphine-dependent rats[1,2,12,20,30]. Collectively, these studies indicate that chronic morphine treatment reduces the activity of noradrenergic neurons which are then activated following administration of an opioid antagonist.

Several investigators have demonstrated that CLON, a partial agonist[3], is effective in ameliorating many of the symptoms of opiate withdrawal in humans[13] and in morphine-dependent rats[11,31]. Several of the effects of CLON appear to be centrally mediated. CLON inhibits the firing rate of LC neurons, which are normally active during morphine withdrawal[1,29] and biochemical studies have shown that CLON may block the increase seen in rat brain NE turnover during opiate withdrawal[10,22]. Since central stimulation of α-adrenergic receptors by CLON results in an inhibition of peripheral sympathetic activity[35], a similar mechanism may be responsible for the inhibitory effects of CLON on the TST response in morphine-dependent rats. This, plus considerable evidence for an action of CLON on pre- and postsynaptic α_2-adrenergic receptors[3] argues that this drug dampens the TST response to NAL by reducing, through and α_2-mediated mechanism, the outflow of NE during withdrawal. However, CLON has been shown also to inhibit firing of serotonin neurons in the midbrain dorsal raphe nucleus[29].

That the reduced TST response to CLON is mediated by damping the central NE hyperactivity during withdrawal is consistent with the ability of phentolamine, an α_1- and α_2-adrenergic antagonist[3], to also attenuate the NAL precipitated TST temperature response in the morphine-dependent rats. By antagonizing both types of adrenergic receptors, phentolamine can attenuate the physiological expression of hyperactivity of the NE neurons during morphine withdrawal. It has previously been demonstrated that the central effects of CLON on adrenergic receptors can be antagonized by α-adrenergic antagonists administered either i.v. or directly into the cerebral ventricles[27]. By inference, since α_2-receptor stimulation antagonizes the TST response, blockade by phentolamine of α_1- (but not α_2-) adrenergic receptors likely located postsynaptically, results in the dampening of the TST response to NAL.

Both phentolamine and CLON have been shown previously to reduce core body temperature in the rat[6,21,32]. This hypothermic effect also is evident in morphine-dependent rats, as has been demonstrated previously with CLON in morphine-dependent rats[31]. Lin et al.[17] reported a similar fall in core temperature of 2 °C with 50 μg phentolamine i.c.v. and 2 mg/kg i.p. in control rats. However, in each of these studies there was an increase in TST of 3–4 °C. In the morphine-dependent rat, we observed a similar fall in core body temperature without the rise in TST. Phentolamine produces its hypothermic effects in normal rats by decreasing metabolic heat production and causing a cutaneous vasodilatation[21]. Since the cutaneous vasodilatory effects of phentolamine are not apparent in the morphine-dependent animal, the fall in core temperature appears to be the result of a decrease in metabolic heat production.

The reduction in core temperature following administration of NAL appears to be dependent on an underlying stimulation of opiate receptors as it does not occur in the normal animal but does in the morphine-dependent or stressed rat[16,23,28]. However, the degree of hypothermia is dose-dependent[18], and is greater following systemic than central administration[17]. This suggests that the effect of NAL on core temperature may be mediated by a mechanism that is different from that which mediates the coincident rise in TST in morphine-dependent rats. The inability of CLON or phentolamine to attenuate the fall in core temperature during the NAL-precipitated withdrawal indicates that this response to NAL may not be mediated by a brain noradrenergic mechanism. This has been suggested previously by Tseng et al.[31] for CLON in morphine-dependent rats. Indeed, it is possible that a portion of the fall in core temperature following NAL administration in morphine-dependent rats may be mediated by a peripheral effect of the narcotic antagonist. We have reported recently that administration of the quaternized form of narcotic antagonists, which do not cross the blood–brain barrier, fail to induce a TST surge but do cause a reduction in core body temperature[17]. Thus, the unexplained differential effect on TST and core temperature following administration with naloxone in the morphine-dependent rat may reflect differing anatomical sites, neurotransmitter, varying sensitivity and/or different responses on heat gain and heat loss mechanism.

Although the α-adrenergic agents were administered centrally we cannot say with absolute certainty that the effects observed are mediated entirely by a central mechanism. However, it has been demonstrated that i.c.v. and not systemic administration of phentolamine blocks the hypothermic effects of CLON[4]. Additionally, Lin et al.[21] reported that a systemic dose of at least 2 mg/kg of phentolamine was needed to achieve a temperature effect in rats similar to that observed by us and Lin et al.[21] following 50 μg i.c.v. administration of phentolamine.

Our observation that the TST surge during precipitated morphine withdrawal is mediated at least in part by an α-adrenergic mechanism may be of importance in understanding the etiology of the menopausal hot flush. CLON[8,25] and α-methyldopa[33] have been reported to reduce menopausal flushing in women and CLON has proven effective in reducing the flush response in a proposed primate model for the menopausal hot flush[15]. Although still speculative, we have reported that the morphine-dependent rat may be a valid model to study the neuroendocrine mechanism leading to the flush response. The data reported herein would add further evidence to the validity of this animal model.

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1S

Prevention of Hot Flushes with CPA in the Hormonal Treatment of Prostatic Cancer Results of a Placebo-Controlled Double-Blind Trial

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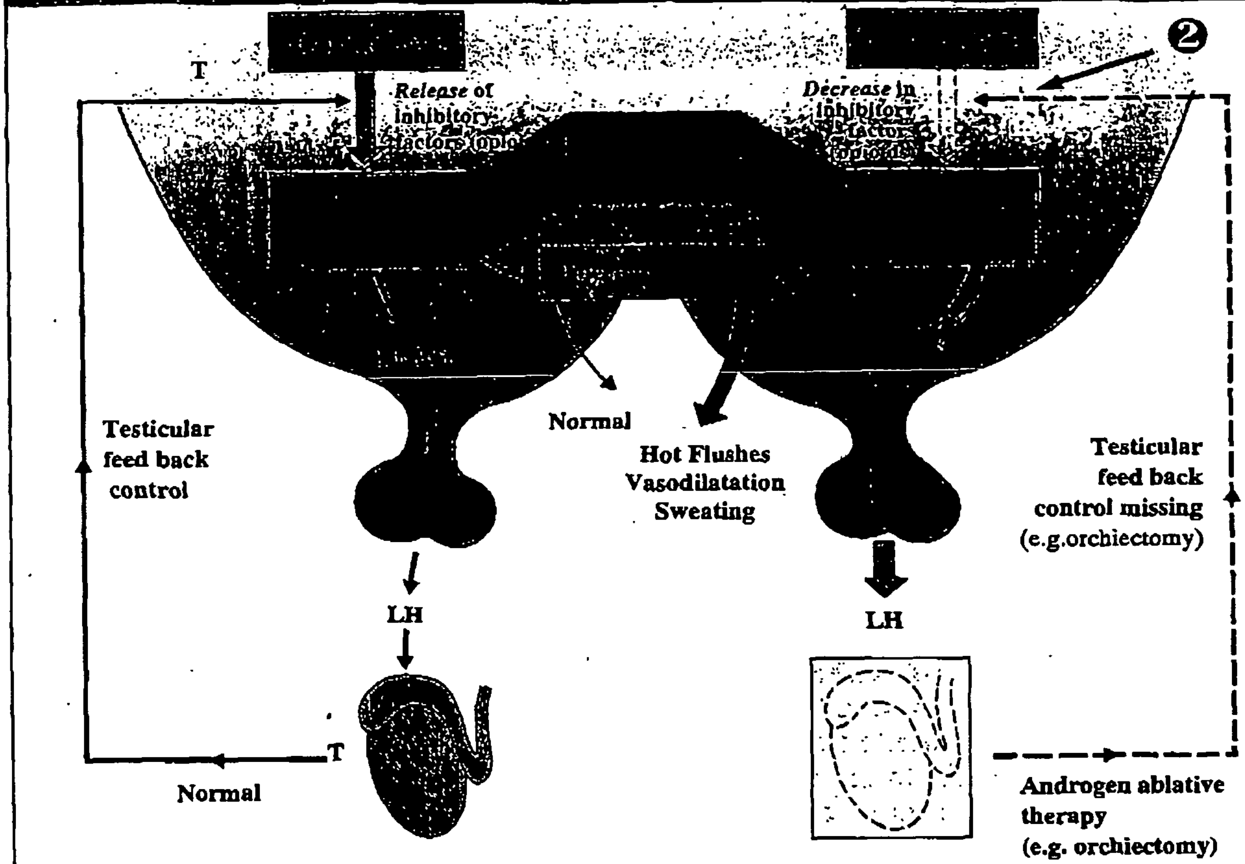
I. INTRODUCTION

Hot flushes (HF) are the most frequently reported side effect, apart from impotence, of androgen ablative therapies for the treatment of prostatic cancer. On average, ***more than 60%*** of these patients suffer from hot flushes [4, 5, 15].

From previous studies it is known that half of these patients are quite inconvenienced by the hot flushes or greatly distressed [2, 8]. The patients experience a sensation of warmth, spreading from the chest to the rest of the body followed by outbreak of sweat (OS) mostly on forehead, chest and back [8]. HF sometimes occur several times an hour, and often they occur at night [9, 10]. Incidence, symptoms and etiology are quite similar to the hot flushes known from menopausal women or following ovariectomy. Numerous implications on the patients' quality of life are known [7, 14]. For instance, HF and OS occurring during the night might cause sleep deprivation. Symptoms observed such as nervousness, easy fatigability, depression or inability to concentrate are considered to be caused by the sleep deprivation following night sweats [13].

HF and OS are caused by the decrease of sex steroids following orchiectomy or therapy with LHRH-agonists. Sex steroids stimulate the release of ***endogenous opioid-peptides*** (EOP) in the hypothalamus (Figure 1). These opioids act as inhibitory factors and suppress the intrahypothalamic release of ***catecholamines***. These catecholamines not only play a role in the feed-back mechanism of LHRH secretion, they furthermore have an influence on thermoregulation. The greatly increased concentration of catecholamines following sex steroid withdrawal causes ***irritations of the thermoregulatory center,*** which is located in close anatomical vicinity to LHRH neurons. This results in a peripheral vasodilatation and HF and OS [1, 8, 12].

It is known that ***cyproterone acetate (CPA),*** like estrogens, has the ability to reduce hot flushes and outbreaks of sweat due to its ***central inhibitory effect.*** In a cross-over trial with 12 orchiectomized patients, treatment with daily 300 mg CPA resulted in a significant reduction in HF when compared to placebo [6]. In another study with orchiectomized patients suffering from HF, dose titration starting from 300 mg CPA was conducted, and for the six patients, a dosage of 100 mg CPA daily already resulted in a significant reduction in frequency of HF [11]. From trials on the treatment of HF in menopausal women, a considerable placebo effect is known [3]. Therefore, a randomized clinical trial of larger scale to compare CPA and placebo regarding the efficacy of reduction in HF and OS was required.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Decrease in inhibitory factors (opioids)
❷
Testicular feed back control
Normal
Hot Flushes Vasodilatation Sweating
Testicular feed back control missing (e.g.orchiectomy)
LH
LH
T
Normal
Androgen ablative therapy (e.g. orchiectomy)

- ***Prevention of hot flushes*** is possible with substances which:

a) ***block adrenergic activity centrally*** (e.g.; Clonidine) ❶ or,

b) which ***reinstate the release of inhibitory opioids*** (e.g., œstrogens, or antiandrogens with an additional central inhibitory effect, such as CPA).❷

II. PATIENTS AND METHODS

A placebo-controlled and double-blind trial including in all 273 patients recruited in 33 urology practices and 15 hospitals was initiated.

The criteria for inclusion were previous orchiectomy, occurrence of hot flushes and/or outbreaks of sweat as well as no further hormonal treatment.

Patients were treated randomly either with 150 mg CPA per day (50 mg t.i.d., n=135) or a placebo (n=138). They were asked for number and degree of severity of HF and OS and adverse events at admission. During the half-year treatment period, patients were controlled again after 6 weeks, 3 and 6 months regarding the occurrence of their complaints. A diary was provided, in which the patients could note the daily number and the degree of severity of their complaints.

The main target variable was the ***number of patients with a reduced number of hot flushes.*** As known from the treatment of HF in climacteric women, a placebo effect of 50-60% was expected, and a 15% better response rate for CPA.

Both groups were comparable regarding age, weight, concomitant diseases and occurrence of HF and OS. Most patients had been orchiectomized only a short time before starting this trial. Their HF had occurred within a few days or weeks after orchiectomy. Other patients had suffered from HF for years.

III. RESULTS

As expected, in both groups the number of patients suffering from HF or OS decreased. As to the number of patients without HF or OS, the difference between the groups is significant during the entire treatment period. After 6 months twice as many patients in the placebo group (6%) as in the CPA group (33%) suffered from HF (Figure 2). For OS, this was the case in 24% of CPA-treated patients and in 47% of placebo-treated patients.

Not only less CPA-treated patients than placebo-treated patients suffered from HF and OS, ***treatment with CPA also resulted in a significantly greater reduction in frequency and in degree of severity of the remaining HF and OS.***

It is of interest that the reason for premature discontinuation in the placebo group in 52% of these cases ***was persistent HF and OS.*** In contrast, in 22% of the CPA-treated group the reason for discontinuation was lack of complaints (Figure 3). Other adverse events reported were comparable in both groups and

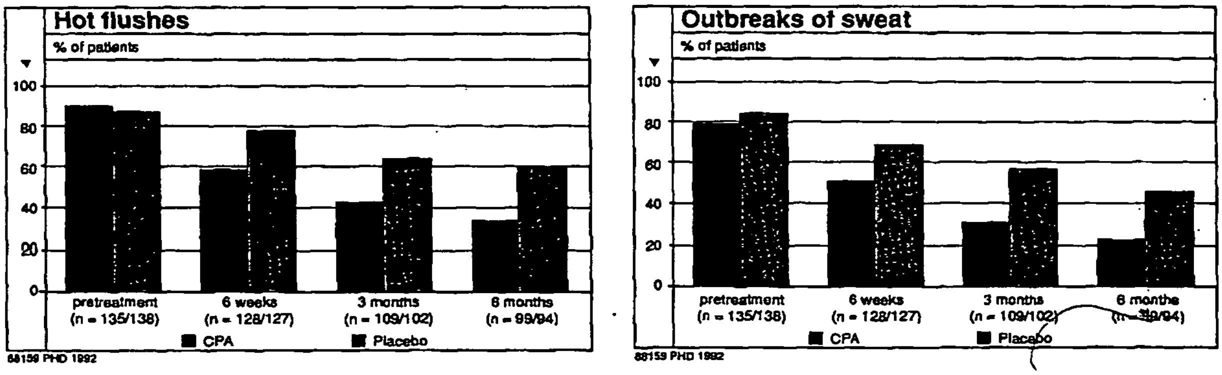


Figure 2 : Hot flushes and outbreak of sweat incidence during 6 months follow up : CPA versus Placebo.

Figure 3 : Reasons for premature discontinuation of treatment in CPA and Placebo groups.

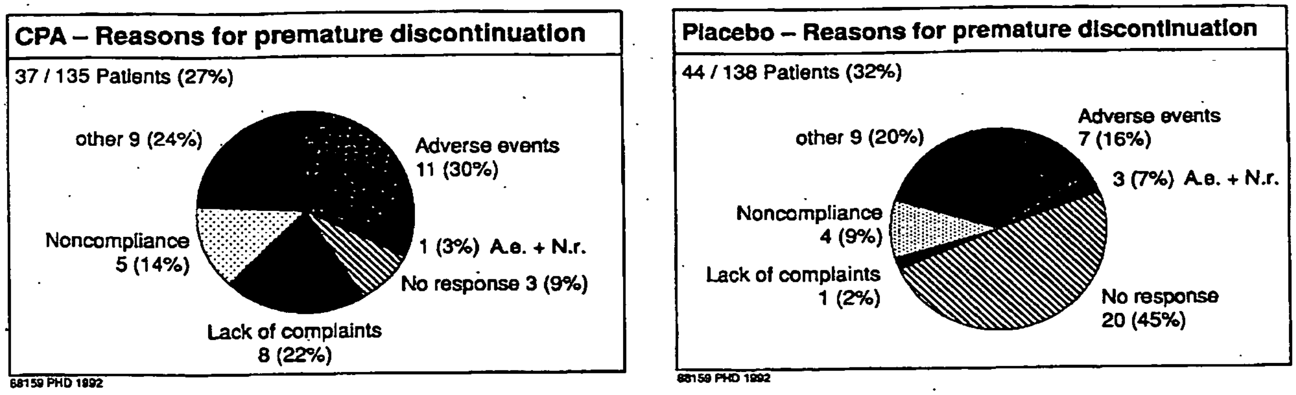
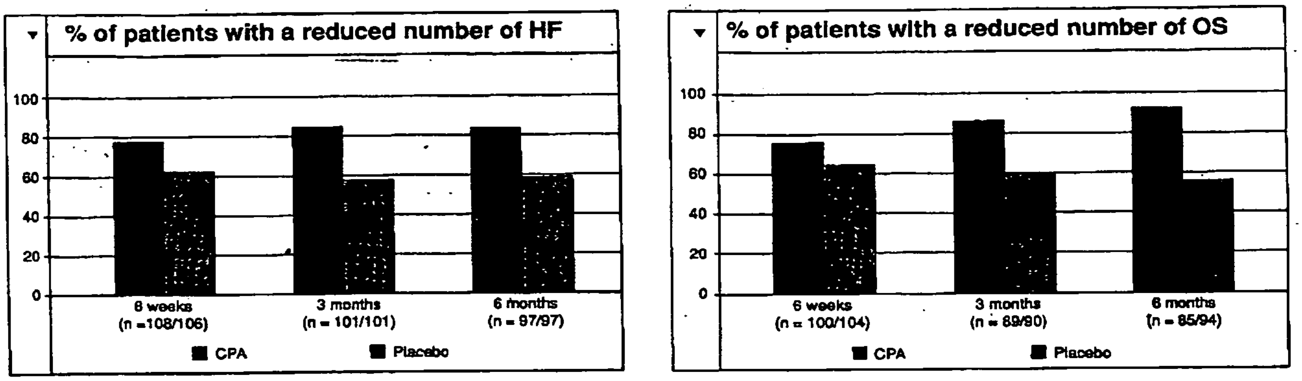


Figure 4 : % of patients with a reduced number of HF and OS : CPA versus Placebo.



gynecomastia and breast tension were the most frequently reported.

The response rate was defined as number of patients with reduction of HF/OS. Patients who withdrew from treatment due to lack of efficacy/complaints were also included in this calculation. The response rate was more than 25% higher in the CPA-treated group after 3 and 6 months when compared to placebo. The difference is significant in each time period (Figure 4).

To summarize the effect of treatment with CPA: many more patients in that group experienced no HF or OS. When patients still suffered from HF and OS, these were reduced with respect to frequency and degree of severity.

IV. CONCLUSION

CPA is a well established androgen ablative agent for prostatic cancer therapy. As demonstrated in this trial, CPA is effective in reducing hot flushes and outbreaks of sweat. These additional effects are an advantage particularly in the palliative treatment of prostatic cancer, where quality of life should be of the utmost importance.

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